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REVIEW

A systematic review via text mining approaches of human and veterinary applications of photobiomodulation: focus on multiwave locked system laser therapy

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Abstract

To evaluate scientific literature regarding the application of Photobiomodulation (PBM), with a special focus on Multiwave Locked System (MLS®) laser therapy, an innovative machine learning method was used. PBM therapy has occurred as a non-invasive therapeutic approach in human and veterinary medicine. It is widely used to treat various musculoskeletal conditions, promote wound healing, and alleviate inflammation and pain through cellular modulation mechanisms.

The methods used were text mining (TM) and topic analysis (TA) to store and process large datasets in digital formats. The investigation followed a systematic approach based on the PRISMA guidelines. Our analysis of 211 selected studies, conducted from 1990 to 2024, identified five key topics in PBM research: therapeutic uses, cellular effects and mechanisms of action, pain control, outcomes in oral pathologies, and laser biostimulation of wounds and bones. Notably, research highlights the effectiveness of MLS® in musculoskeletal pain management, neuropathic conditions, and complex wound care, both in human and veterinary medicine. Despite increasing evidence supporting its clinical applications, significant gaps remain regarding standardized treatment protocols and a deeper understanding of molecular mechanisms.

Further research is necessary to elucidate optimal parameters for different clinical applications, with particular emphasis on individualized dosing, frequency, and treatment duration, to maximize therapeutic outcomes.

Keywords Photobiomodulation · Multiwave-locked system · Laser therapy · Text mining · Topic analysis

Introduction

Photobiomodulation (PBM) encompasses various non-invasive therapies involving biological tissue irradiation with light at specific wavelengths. This technique employs light sources, such as lasers and light-emitting diodes (LEDs), primarily within the visible and infrared spectrum. PBM therapy has been widely tested for its potential to modulate cellular processes, promote tissue repair, reduce inflammation, and alleviate pain [1].

In human medicine, it has been employed in the treatment of a wide range of conditions, such as chronic pain, wound healing, and musculoskeletal disorders [2]. In veterinary medicine, PBM has been predominantly used in both small and large animals to treat musculoskeletal injuries and neurological disorders, and in wound management [3].

Biological effects and mechanisms of action of PBM

PBM exerts its biological effects by stimulating chromophores within cells, particularly in the mitochondria.

By utilizing specific wavelengths of light to target tissues, PBM can stimulate biological processes reducing inflammation, alleviating pain, and enhancing cellular metabolism. While early interpretations suggested wavelength-specific effects, current understanding acknowledges that a variety

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of wavelengths may produce similar outcomes, provided that dosimetry is appropriately adjusted to account for the energy profile and optical behavior of each wavelength [4]– [5]. These outcomes are also influenced by wavelength-dependent tissue interactions, including attenuation, scattering, and absorption phenomena.

It has been suggested that PBM activates cellular signaling pathways and promotes the production of key molecules that support healing and tissue regeneration [6].

Despite these insights, the exact mechanism underlying light therapy remains poorly understood.

One theory proposes that photons interact with mitochondrial chromophores, especially cytochrome c oxidase (CCO), leading to the photodissociation of nitric oxide (NO). This process enhances electron transport, enzyme activity, and ATP production, which contribute to cellular repair and regeneration [1].

Recent evidence highlights additional photoreceptors involved in PBM, such as opsins and transient receptor potential (TRP) ion channels, which are sensitive to light or heat and may influence cell depolarization and signaling [7]– [8].

Chromophores like flavins, flavoproteins, and interstitial water may also play roles in PBM responses [9]. Redox reactions triggered by light exposure affect the cellular redox balance and influence gene expression and the synthesis of nucleic acids [10]. The release of NO from CCO enhances mitochondrial function and ATP production [11]. Reactive oxygen species (ROS), generated at low levels, act as secondary messengers in signaling cascades, rather than as cytotoxic agents. These molecular events lead to physiological outcomes such as improved wound healing, pain reduction, modulation of inflammation, enhanced muscle recovery, and neuroprotection following traumatic injury or stroke [12].

Light-sources characterization

A wide variety of light-emitting sources are routinely utilized in clinical settings that comprehend the use of PBM. Red and near-infrared (NIR) are wavelengths most commonly used, although blue has been reconnoitered more recently for the treatment of superficial tissues. NIR is generally preferred for deeper tissue treatments due to its relatively lower absorption of the main absorbing molecules and less scattering compared to shorter wavelengths.

Nonetheless, recent studies indicate that over 90% of NIR energy is absorbed within the first 10 mm of biological tissue [13–15]. This presents a challenge for treating targets located beyond this depth. While it has been hypothesized that short pulses with high peak power could facilitate deeper photon delivery, it has been demonstrated that peak power alone is not a reliable determinant of effective energy deposition at depth, as differences in irradiance between low- and high-peak power systems tend to diminish due to scattering and absorption [13–15].

However, under specific conditions—such as those involving extremely short pulse durations, low duty cycles, and sufficient peak power, as demonstrated in the EMS 905 nm system studied by Kaub [13]– [14] —residual optical energy has been detected at depths up to 20 mm, at levels potentially relevant for biological activation. Although clinical implications remain to be established, this suggests that certain delivery strategies may help overcome some of the inherent optical limitations [13–15].

Based on the power of the emitted light lasers used in PBM treatment are classified into low-level laser therapy (LLLT) and high-power laser therapy (HPLT). LLLT refers to the use of lasers with an average beam power of less than 500 mW, used primarily for superficial tissues, and it is used to treat inflammatory processes and alleviate pain, while, HPLT, due to beam power greater than 500 mW, penetrates deeper tissues and is utilized for more significant therapeutic interventions, such as managing chronic pain and extensive musculoskeletal damage [12].

In recent years, the use of class IV high-power laser therapy (HPLT) devices has become increasingly common in both human and veterinary medicine. These systems can deliver high output powers, often in the range of 10–30 W or more; however, energy is typically applied over large areas using broad optical spot sizes and scanning techniques to maintain average irradiance within safe and biologically tolerable limits. Continuous lasers may deliver average irradiances of 30–100 mW/cm², while pulsed lasers can reach very high peak powers—up to 270 W/cm² or more—without exceeding thermal thresholds, due to the use of short duty cycles or gated emission modes. Some high-intensity systems, such as the Hiro® by ASA Laser and the Fotona Litewalker (Nd: YAG free-running pulsed system), can theoretically exceed 10,000 W/cm² in peak irradiance; however, the effective dose reaching the tissue remains controlled to avoid surface overheating, ensuring that tissue temperatures remain below 45 °C. For example, in the study by Looney et al. (2018), although a laser with a peak output capacity of 12 W was used, the energy was delivered over large areas (125–350 cm²) using a scanning technique, resulting in an estimated average irradiance of approximately 28–40 mW/cm². This highlights that peak output power alone is not indicative of the true irradiance delivered to the tissue, which depends on several factors including spot size, scanning speed, and emission mode.

In veterinary medicine, despite their frequent use, a lack of consensus on the most effective treatment protocols and therapeutic efficacy remains [12].

Several key parameters influence the clinical outcomes of Photobiomodulation Therapy (PBMT). One of the primary factors is the wavelength of the light, which affects tissue penetration and the biological response, followed by the beam coherence. While laser light is coherent (with waves in phase), LED light is typically non-coherent; however, both types are used in the treatment with PBMT [16].

Also, the therapy's effectiveness is determined by the energy of the light beam and the power. The dose of light and the irradiance or power density, influence significantly tissue response to treatment. Additionally, the emission modality of the light source (continuous, frequency-based, or pulsed) may modulate the biological effects of PBM [17].

The overall success of PBMT is also affected by the total number of treatment sessions and the intervals between them, which determine the cumulative therapeutic impact on the tissue [12, 18]. Proper adjustment and combination of these parameters are essential for achieving the desired clinical outcomes.

PBMT typically follows a biphasic dose-response pattern; for certain purposes lower doses may be more effective than higher doses, indicating the need for an optimal dose tailored to each clinical scenario. Research regarding PBMT of chronic musculoskeletal pain in humans has shown improved outcomes with treatments employing higher power densities and consistent scheduled treatment.

Effective wavelengths for PBMT generally fall within the "optical window" range of 600 to 1070 nm. Lower wavelengths (600 to 700 nm) are typically used for targeting superficial tissues, while higher wavelengths (780 to 950 nm) are more suited for deeper tissue penetration [12, 18].

As highlighted by Zein et al. (2018) [19], for near-infrared PBM therapies, peak irradiance should generally remain below 750 mW/cm² to prevent undesired photothermal effects. Nevertheless, devices employing pulsed or gated emissions can achieve high peak powers while maintaining a low average irradiance, especially when combined with large spot sizes and continuous motion scanning. These delivery strategies are designed to keep tissue temperatures below 45 °C, minimizing the risk of heat-induced cellular damage.

Cronshaw et al. (2023) [20] further analyzed the photothermal behavior of high-intensity PBM systems, emphasizing that thermal safety is influenced not only by output power but also by beam geometry, spot profile (Gaussian vs. flat-top), and exposure time per unit area.

MLS® laser therapy

Among the various types of lasers, Multiwave Locked System (MLS®) represents a family of high-power, non-invasive, class IV therapeutic lasers. MLS® laser therapy has been reported to provide therapeutic benefits in clinical settings, particularly in pain relief and inflammation control, though further independent studies are warranted to fully establish its comparative effectiveness [21].

MLS® devices emit two different wavelengths within the NIR spectrum: 808 nm in continuous or frequency-modulated mode, and 905 nm in pulsed mode. The device configuration, protected by a technical patent from ASA srl, enables spatial and temporal synchronization of these two emissions. Although other manufacturers also employ dual-wavelength or coaxial emission systems, MLS® has been investigated in both clinical and preclinical settings. For example, Corti et al. [22] demonstrated improved clinical outcomes in patients with cervical pain using synchronized dual-wavelength therapy, while Gigo-Benato et al. [23] reported enhanced nerve regeneration in vivo compared to either wavelength alone. While these results are promising, further independent validation is needed to determine whether synchronization confers unique therapeutic advantages compared to other PBM configurations.

Mechanistically, the 808 nm wavelength has been shown to increase mitochondrial respiratory chain activity by targeting a secondary absorption peak of cytochrome c oxidase, while the 905 nm wavelength affects complexes I–IV and succinate dehydrogenase [24].

It has been hypothesized that combining these wavelengths may offer broader or synergistic biological effects compared to single-wavelength LLLT [25].

MLS® therapy has also been associated with the stimulation of angiogenesis, enhancement of cellular energy production, regulation of inflammatory processes, and modulation of fibroblast activity. Additionally, some reports note reduced treatment times with MLS® systems, which may facilitate integration into clinical practice, though these findings require further investigation [25].

Objective of the study

This study conducts a systematic review of research on PBMT, with a particular focus on PBMT utilizing MLS® lasers, by employing text mining (TM) and topic analysis (TA) approaches to store and process data in digital formats. The primary rationale for using data mining techniques is their ability to efficiently store and process large datasets in digital formats. TM provides a method for exploring unstructured data, reducing errors and time expenditure while yielding more accurate insights [26].

The primary aim of this study is to identify prevailing research topics related to the use of PBMT in both human and veterinary medicine, with particular emphasis on MLS® lasers. Additionally, the secondary objectives are to provide an overview of the temporal trend of these topics, interpret their evolution over the past century, and identify potential research gaps.

Methods

Literature search and descriptive statistics

A systematic review of scientific literature was conducted to classify articles with at least an English abstract on the topic of PBMT in both humans and veterinary medicine, with a specific focus on the MLS®. The exploration was achieved using the Scopus® database, recognized for its complete reportage of academic literature [27].

The search and analysis were carried out on June 13th, 2024, and developed considering on the year of publication (from 1990 to 2024), article type (review and scientific article), language (English), and availability of the abstract. The keywords used in the search included: "photobiomodulation AND MLS", "photobiomodulation AND laser AND medicine", "MLS AND therapy", "MLS AND medicine" and "Multiwave Locked System AND laser".

A Microsoft Office Excel® spreadsheet containing all records retrieved from Scopus® was generated. Each row in the spreadsheet represented a document, and the columns contained detailed information such as the authors, affiliations, abstracts, year of publication, document type (e.g., article or review), source of publication (e.g., Journal title), and topic covered.

The records were initially selected, and those without an abstract, or not classified as articles or reviews (e.g. book chapters, conference papers, errata, letters, notes, short reviews), as well as those lacking authors information, non-English texts (i.e. Bosnian, Chinese, Croatian, Danish, French, German, Hungarian, Japanese, Korean, Romanian, Russian, Slovak, Spanish, Turkish) and duplicate entries were automatically excluded.

The research team (APr-AP-VB-MP) then independently reviewed the titles and abstracts of the 763 records. Any discrepancies in the selection process were addressed through team discussions until consensus was achieved. In cases of disagreement, the team used collaborative discussions to decide which articles would proceed to full-text screening. Subsequently, the full-text articles were independently assessed by the researchers for potential inclusion, with any further disagreements resolved through discussion to reach a final decision on inclusion or exclusion.

Records related to other types (e.g., surgical lasers), or non-medical uses of lasers (e.g. application in sports or exercise) were excluded. Additionally, articles referring to "MLS" in non-relevant contexts, such as "Medical Laboratory science", "moving least squares", "mucinous cystic lesions", "Magnetoliposomes", "maximum LOD score", "midline shift", "Macrocyclic lactones", "medication liaison services", "multilevel scheme", Multinomial logit specification", "Mulisan decoction", "mistletoe lectins", "Motorische Leistungsserie", "Machine Learning System", "multilevel surgery", "menopause-like syndrome", "Marine–Lenhart's syndrome", "Middle lobe syndrome", "Massage-like stroking", "Microphthalmia with linear skin defects syndrome", "Macrophage-like", "Morel-Lavallée seroma", "Marine-Lenhart Syndrome", "Major League Soccer", "McLeod Syndrome", "ML scanner" or "Myxoid liposarcom", were eliminated from the dataset (Table 1).

Text mining has proven to be a useful instrument in systemic reviews for detecting publication bias and reducing the likelihood of overlooking relevant documents [28]. To minimize potential bias in this review, a dual approach was

Table 1 Inclusion and exclusion criteria applied to the screening phase

Inclusion criteria (labels)	Explanations
Language	*English*
Years	*1900–2024*
Topic	*Photobiomodulation in humans and in veterinary medicine with multiwave locked system*
Source	*Articles and/or Reviews*
Available	*Abstract*, *full text*, *Authors*, *Journals*
Exclusion criteria (labels)	Reasons
Other types of lasers	*Reports about other types of lasers (i.e. surgical, etc.)*
Other types of use	*Reports about no medical use of lasers (i.e., in sports, etc.)*
MLS such as other acronymous	*Acronymous excluded: "Medical Laboratory science", "moving least squares", "mucinous cystic lesions","Magnetoliposomes", "maximum LOD score","midline shift", "Macrocyclic lactones", "medication liaison services", "multilevel scheme", Multinomial logit specification", "Mulisan decoction","mistletoe lectins", "Motorische Leistungsserie","Machine Learning System", "multilevel surgery","menopause-like syndrome", "Marine–Lenhart's syndrome",""Middle lobe syndrome", "Massage-like stroking","Microphthalmia with linear skin defects syndrome", "Macrophage-like", "Morel-Lavallée seroma", "Marine-Lenhart Syndrome", "Major League Soccer", "McLeod Syndrome", "ML scanner" or "Myxoid liposarcom"*

employed, integrating text mining with manual selection conducted by the authors.

The flowchart (Fig. 1) shows each step of the procedure, displaying the number of records retained for further analysis or removed from consideration. A total of 948 records were selected for review.

Preliminarily descriptive statistics were performed to generate a exhaustive report of the scientific dataset. Pivot tables were used to define the yearly publication count and to identify the principal journals contributing to the field.

Text mining

Following the selection of the articles for analysis, Rstudio (Version 1.3.1093, Free Software Foundation, Boston, MA, USA) was used to conduct the text mining analysis in R.

A dedicated Excel spreadsheet was generated with two columns: "doc_id", which assigned sequential numbering to the 211 selected documents, and "text," which contained the abstracts of these papers for TM analysis.

The body of documents underwent several pre-processing steps as described previously [29]. First, the text was converted to lowercase, and unusual symbols (e.g., *"@"*, *"/" or "*"*), punctuations, numbers, and stop words (e.g. *"the"*, *"a"*, *"and"*, *"or"*, *"on"*, *"for"*, etc.) were removed.

Additionally, the authors manually excluded words directly related to the research topic or commonly used terms, such as *"laser"*, *"disea"*, *"applic"*, *"differ"*, *"level"*, *"group"*, *"heal"*, *"light"*, *"review"*, *"article"*, *"treatment"*, *"multiwave"*, *"locked"*, *"system"*, *"lllt"*, *"photobiomodulation"*, *"photomodulation"*, *"medicine"*, *"veterinary"*, *"mls"*, *"PMBT"*, *"therapy"*, *"patient"*, *"signifi"*, *"therapy"*, *"clinic"*.

Any extra white spaces created during the previous steps were also eliminated. Finally, text tokenization was achieved to abbreviate words to their root forms.

A document-term matrix (DTM) was then created, with documents organized in rows and terms in columns. To access the significance of each word, the term frequency-inverse document frequency (TF-IDF) method was employed. This method assigns comparative loads to words, pondering both their frequency within a document and their occurrence through the articles' assemblage. The TF-IDF adjustment allowed for a more accurate evaluation of word importance within the dataset, with words having a TF-IDF score greater than > 1.5 visualized in a histogram.

Additionally, a word cloud was generated using the website https://www.wordclouds.com/, where larger font sizes corresponded to higher TF-IDF values, representing the most significant terms. Based on a correlation level of ≥ 0.2, links between the most significant words (TF-IDF > 1.5) and all other terms within the body were recognized. Statistical analysis was conducted using R (2017) and included

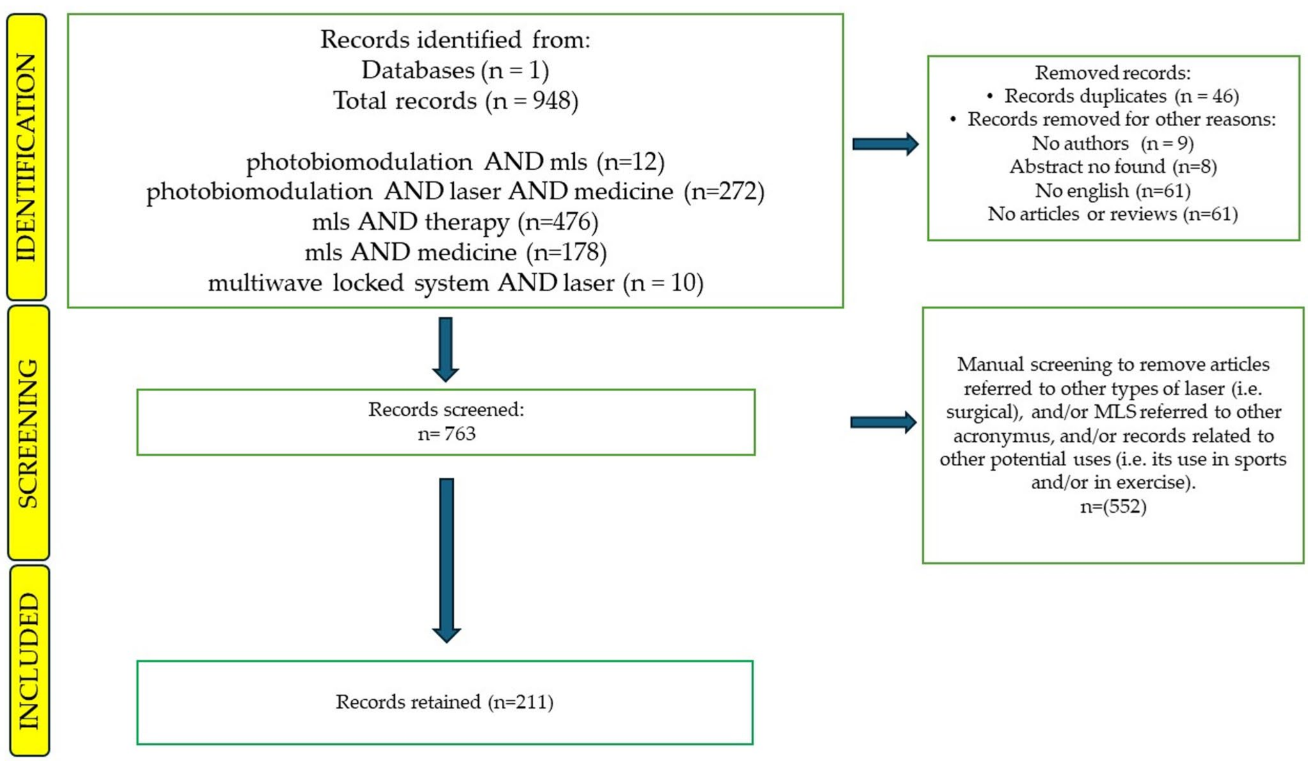

Fig. 1 Flowchart illustrating the process of analysis used

relevant packages and functions such as “tm,” “SaeballC,” “ggplot2,” “delve,” and “tidyverse.”

Topic analysis

For the Topic Modelling Analysis, the Latent Dirichlet Allocation (LDA) approach was employed. LDA is a hierarchical Bayesian method that recognizes thematic issues by examining word co-occurrence patterns within texts [30]. Each topic is characterized by a multinomial distribution of words, while and each text is represented by a multinomial distribution of latent topics. Through the analysis of the detected texts and word frequencies, the model exposes the main subject organization, generating topic distributions for each document and word distributions for each topic [31, 32]. The LDA model was implemented using a Gibbs sampling function from the “topicmodels” package in R. The most common words for each topic and their comparative possibilities were envisaged using the “tidytext” library in R.

Before running the analysis, the optimal number of topics had to be determined, as it is generally unknown. The authors experimented with dividing the corpus into 4, 5, 6, and 7 topics, ultimately choosing the most informative set based on agreement. The research group agreed on five distinct topics, assigning indicative labels to each after deliberation.

To rank the issues, cumulative possibilities of the top 10 words in each topic were considered, and the topics were then showed according to this ranking. Each topic was visualized in a bar histogram, where each bar represents the probability of a word occurring within that topic, measured by the beta-value coefficient. This method facilitated topic identification and labeling, following the approach outlined by Nalon et al. [33].

Results

Descriptive statistics

Out of 948 abstracts downloaded by Scopus, 211 (22.25%) met the screening and eligibility criteria and were engaged for analysis. Articles that were excluded included those concerning other types of lasers, non-medical use of lasers, or those “MLS” referred to other acronyms (58.22%; n=552). Additional exclusions were due to duplicates (4.85%; n=46), lack of an abstract (0.84%; n=8), absence of an author (0.94%; n=9), non-English full-text availability (6.32%; n=60), and records that were not categorized as articles or reviews (6.43%; n=61).

The retained records consisted of research articles (152/211; 72.03%) and reviews (59/211; 27.96%). Of the 211 articles, 17.54% (n=37) focused on studies involving animals, while the remaining 82.46% (n=174) were based on human studies. The total number of records published per year has shown a marked increase over the last decade.

A total of 31.28% of the records featured the first authors from Europe, establishing it as the leading region for research on the topic. In comparison, Asia, North America, South America, Oceania, and Africa contributed progressively smaller percentages of records, with 28.44%, 18.96%, 15.16%, 3.32%, and 2.84%, respectively. These findings are illustrated in Fig. 2. Especially, the United States accounted for 15.16% of the articles, followed by Brazil at 14.22% and Italy at 8.53%, making these three countries the most prominent contributors to the published literature on this issue.

The records included were published in 123 different scientific journals. The journals with more than five articles on the topic include Lasers in Medical Science, (with 23/211 records; 10.90%), Photobiomodulation, Photomedicine, and Laser Surgery (13/211 records; 6.16%), Lasers in Surgery and Medicine (11/211 records; 5.21%), International Journal of Molecular Sciences (6/211 records; 2.84%) and Photomedicine and Laser Surgery (6/211 records; 2.84%), and the Journal of Lasers in Medical Sciences (5/211 records; 2.36%).

Table 2 highlights the most cited publications over the past ten years, providing details on the titles and the number of citations for each article.

The four most cited publications on Photobiomodulation Therapy (PBMT) in the last decade highlight key research areas within medicine and dentistry:

(i) “Photobiomodulation—Underlying Mechanism and Clinical Applications” [1]– This study, with 263 citations, is the most cited and explores the mechanisms by which PBMT interacts with stem cells, enhancing repair processes.
(ii) “Craniofacial Wound Healing with Photobiomodulation Therapy: New Insights and Current Challenges” [34]- The second most cited article, with 115 citations, focuses on craniofacial wound healing. This paper suggests a shift from traditional prosthetics to biological repair methods.
(iii) “Photobiomodulation Therapy for Wound Care: A Potent, Noninvasive, Photoceutical Approach” [35].– This third most cited article (114 citations) highlights the versatility of light devices for wound management.
(iv) Hou et al. [36]– The fourth most cited article, with 100 citations, examines PBMT’s moderate benefits in treating chemotherapy-induced peripheral neuropathy.

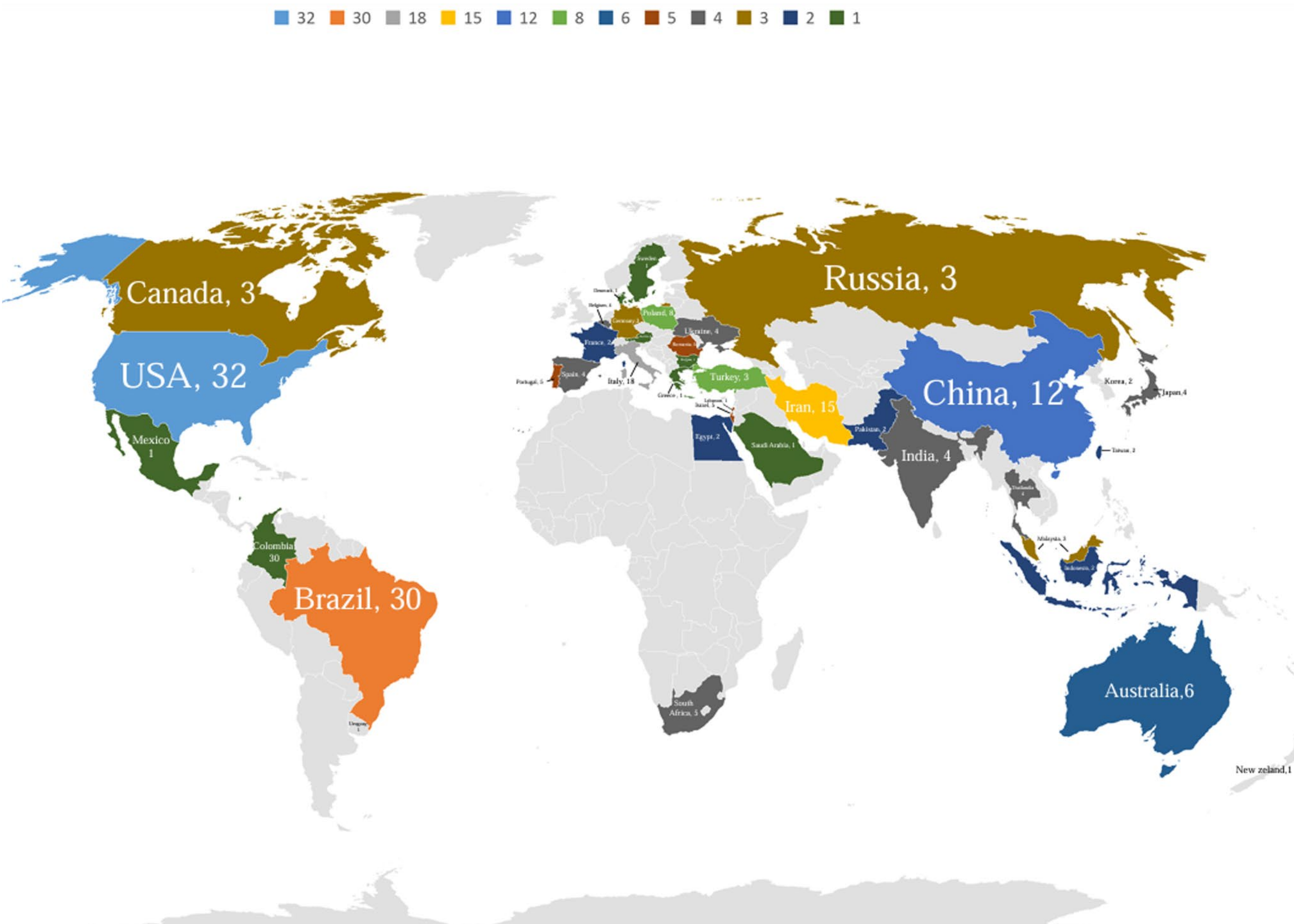

Fig. 2 Map of number of peer-reviewed articles published worldwide by country

Table 2 The most cited documents referred to the interval of years between 2014–2024

No.	Authors/Year/Journal	Title of publication	Total citations
1	Dompe et al., 2020; Journal of Clinical Medicine	Photobiomodulation - underlying mechanism and clinical applications	263
2	Arany, 2016; Journal of Dental Research	Craniofacial Wound Healing with Photobiomodulation Therapy: New Insights and Current Challenges	115
3	Mosca et al., 2019; Advances in Skin and Wound Care	Photobiomodulation Therapy for Wound Care: A Potent, Noninvasive, Photoceutical Approach	114
4	Hou et al., 2018; Pain Physician	Treatment of Chemotherapy-Induced Peripheral Neuropathy: Systematic Review and Recommendations	100

These articles underline PBMT's expanding applications, particularly in wound healing, stem cell-based repair, and neuropathy treatment.

Looking more closely at the MLS-focused studies, they account for 13.27% ($n=28$) of the articles. They are distributed as follows:

(i) more than half (57.14%; $n=16$) in human medicine (on pathologies such as Bell's palsy, oncological diseases, osteoarthritis, osteoporosis, subacromial pain syndrome, chronic neck pain, knee joint pain, Raynaud's disease, scoliosis and Covid19);

(ii) 28.58% ($n=8$) preclinical studies, of which 75% ($n=8$) in cell culture (liposomes, erythrocyte membranes, human mesenchymal stromal cells) and 25% ($n=2$) in rats (neuropathic pain studies);

(iii) 7.14% ($n=2$) in veterinary medicine (on dogs and sheep).

(iv) 7.14% ($n=2$) are reviewed in human medicine explicitly referring to the MLS system. These articles underline PBMT's expanding applications, particularly in wound healing, stem cell-based repair, and neuropathy treatment.

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Text mining results

Following the data pre-processing and sparseness reduction steps in the study, a total of 1230 terms were retained from the 211 records. The TF-IDF method recognized the most relevant words, which are visualized in Fig. 3 as a word cloud where the size of each word correlates with its TF-IDF value, providing a visual representation of the most important terms.

Fig. 3 Cloud representation of most relevant database words (TFIDF ≥ 1.5). Their size reflects the relative importance of the terms

The terms with the highest TF-IDF scores, indicating their prominence across the records, include: *"cell"*, *"pain"*, *"wound"*, *"oral"*, *"bone"*, *"tissue"*, *"diabet" (diabetes)*, *"skin"*, *"injuri" (injury)*, *"irradi" (irradiation)*, *"improv" (improvement)*, *"function"*, *"acupunctur" (acupuncture)*, *"increa" (increase)*, *"differenti" (differentiation)*, *"report"*, *"evalu" (evaluation)*, *"regen" (regeneration)*, *"month"*, *"therapeut" (therapeutic)*, *"muscl" (muscle)*, *"control"*, *"score"*, *"evid" (evidence)*.

The most relevant words tended to cluster together, showing patterns of co-occurrence in the abstracts. Notably, the key word associations are as follows:

1. *"acupunctur"*, *"applic"*, *"bone"*, *"cell"*, *"clinic"*, *"diabet"*, *"differ"*, *"differenti"*: Words like "acupunctur" and "bone" often appear alongside references to "cell", "clinic", and "diabet", pointing towards studies on clinical applications and cellular responses, particularly in the context of bone and diabetes research.
2. *"diseas"*, *"function"*, *"group"*, *"heal"*, *"improv"*, *"increas"*, *"injuri"*, *"irradi"*: This cluster suggests a focus on tissue healing, improvement of function, and irradiation-based therapies for various diseases and injuries.
3. *"level"*, *"oral"*, *"pain"*, *"patient"*, *"signific"*, *"skin"*, *"tissu"*, *"wound"*: Here, the terms "pain", "patient", "wound", and "tissue" are associated with significant clinical outcomes, highlighting a concentration on pain management, wound healing, and skin-related treatments.

Table 3 provides the specific correlations (with a correlation grade ≥ 0.2) between the most relevant words (with TF-IDF ≥ 1.5) and the remaining terms. These correlations help in understanding the underlying themes by revealing how frequently certain words co-occur within the document corpus. This approach ensures a clearer depiction of the significant topics being researched in the field of PBMT, especially using MLS® lasers.

The analysis underscores PBMT's relevance to tissue repair, pain management, and regeneration, aligning with its wide-ranging applications in both human and veterinary medicine.

Topic analysis results

The systematic review identified five main topics related to PBMT through topic modeling, with each topic addressing different aspects of PBMT research. These topics were analyzed based on the number of records associated with them, their first publication year, and their cumulative probability (CP) rankings (see the Table 4 below).

Figure 4 shows the topics ranked based on their cumulative probability (CP), which reflects their prominence within the corpus of reviewed studies. Topic 1 (PBM Therapeutical Uses), Topic 4 (Pain Control with PBM), and Topic 2 (PBM Effects on Cells and Its Mechanism of Action) were ranked highest by CP, suggesting that these areas have garnered the most attention in research.

Figure 5 illustrates the annual distribution of articles published within each topic from 2000 to 2024. Across all five topics, a notable upward trend in the number of published studies is evident, particularly in the last decade. This increase signifies growing interest and expanding research in PBMT applications, especially in pain management, tissue regeneration, and therapeutic interventions.

This review underscores the diverse and evolving nature of PBMT research, with a clear focus on exploring its

Table 3 Associations between the most relevant words (with TFIDF ≥ 1.5) and the remaining words of the matrix

Words (TF-IDF ≥ 0.1)	Associated words (correlation ≥ 0.2)
Acupunctur	histori (0.56); electroacupuncture (0.52); ultim (0.46); administ (0.45); resolute (0.45); administr (0.44); begin (0.43); definit (0.43); sign (0.40)
Applic	deliver (0.46); dentistry (0.46); analgesia (0.44); inform (0.40)
Bone	Deposit (0.60); scaffold (0.58); biocompat (0.57); cortic (0.55); euthanasia (0.55); defect (0.54); marrow (0.43); biomateri (0.42); biopolym (0.42)
Cell	stem (0.71); regen (0.46); prolifer (0.43); mesenchym (0.42); osteoblast (0.42); vitro (0.42)
Diabet	Closur (0.56); mellitus (0.53); complic (0.41); apoptosis (0.40)
Differenti	Neuron (0.63); neural (0.59); adiposederiv (0.57); admsc (0.48); vitro (0.46); stem (0.44)
Group	Receiv (0.42); week (0.41)
Health	Cutan (0.48); nonirradi (0.41); histology (0.40)
Increase	physiolog (0.51); product (0.48); enzymat (0.46)
Injuri	Acut (0.43)
Irradi	Mwcm (0.46); density (0.43); dose (0.42); energi (0.42); viabil (0.32); emit (0.41); mscs (0.41)
Level	Crucial (0.52); acid (0.46); variety (0.44); protein (0.40)
Oral	Mucos (0.66); cavity (0.57)
Skin	Penetr (0.62); width (0.55); versus (0.53); depth (0.51); equip (0.49); ultrasonographi (0.49); acquir (0.47)
Wound	Histologic (0.61); econom (0.51); cutan (0.47); faster (0.43); cytokine (0.41).

Table 4 List of topics, number of records contained and first year of publication

Topic number	Label of the topic		Papers (n)/from year
1	PBM therapeutical uses		52/2006
2	PBM effects on cells and its mechanism of action		40/2009
3	Outcomes of PBM (i.e. in oral pathologies)		39/2014
4	Pain control with PBM		50/2003
5	Laser PBM on wounds and bones		30/2004
Topic Name	***N*° of Records**	**First-Year Publication**	**Key Focus**
Topic 1: PBM Therapeutical Uses	52	2005	Medical applications of PBMT in various therapeutic areas.
Topic 2: PBM Effects on Cells and Its Mechanism of Action	40	2003	Cellular effects and mechanisms of PBMT, especially in tissue regeneration.
Topic 3: Outcomes of PBM in Oral Pathologies	39	2007	PBMT in dentistry for oral health, tissue regeneration, and wound healing.
Topic 4: Pain Control with PBM	50	2004	Use of PBMT in managing and alleviating pain, especially in chronic conditions.
Topic 5: Laser PBM on Wounds and Bones	30	2000	PBMT's role in wound healing and bone regeneration.

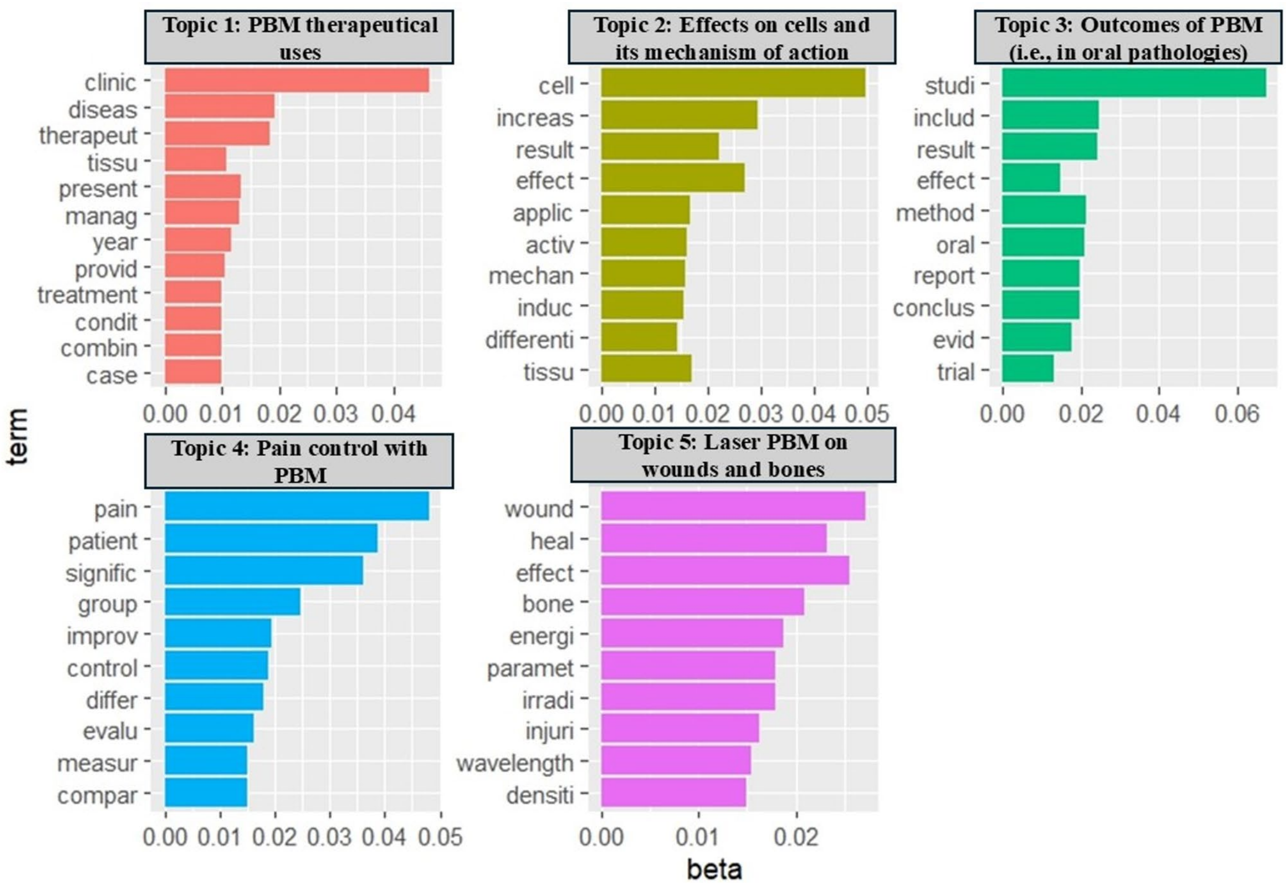

Fig. 4 The topics numbered from 1 to 5 according to the cumulative probabilities (cp.), and the first 10 words for each topic numbered from 1 to 5 according to the cumulative probabilities

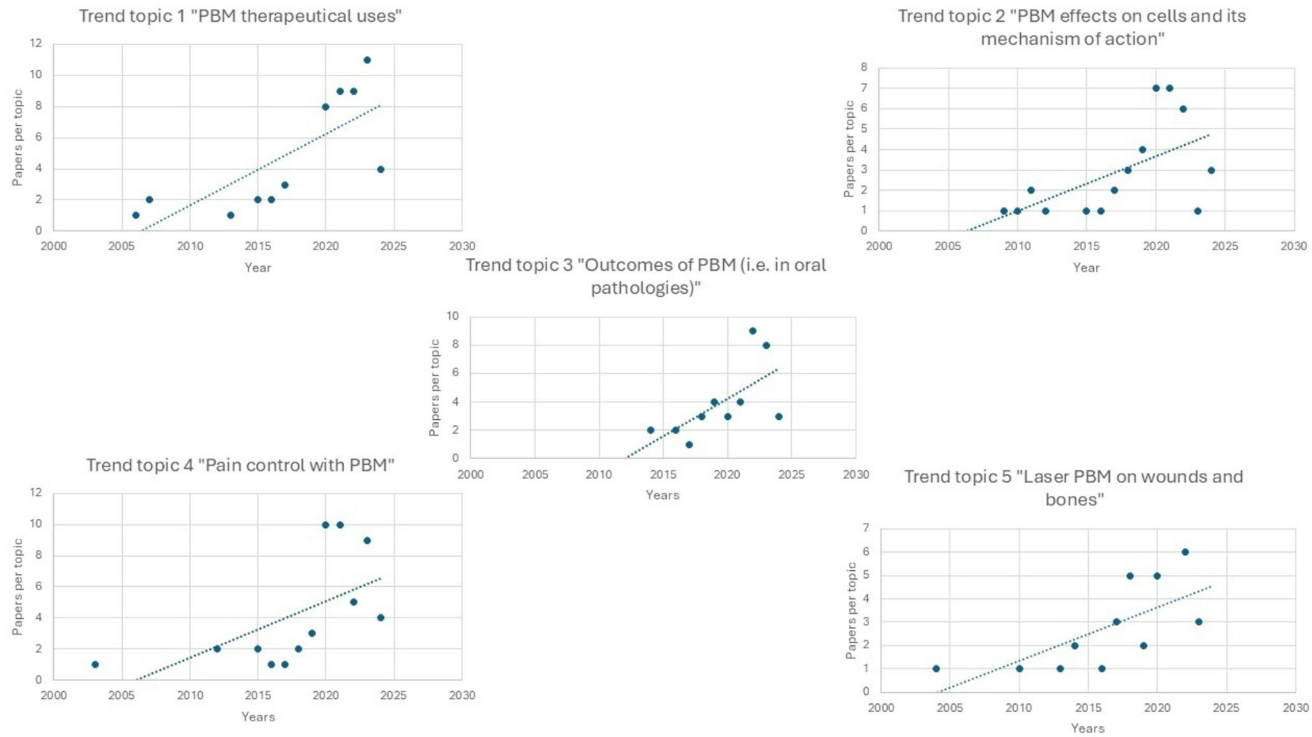

Fig. 5 Number of articles included for each topic from the first year of publication and topics' trendline

therapeutic potential, particularly in pain control and tissue repair, using MLS® lasers and other modalities. The upward trend in publications further emphasizes PBMT's expanding role in clinical and veterinary medicine.

Discussion

This study explored the possible application of PBM in both human and veterinary medicine with a special focus on the MLS® laser therapy. By thoroughly examining the body of research, the Authors gained deep insights into the complexities of the field. Additionally, these methodologies helped identify areas with limited understanding and gaps in knowledge.

The number of published articles on PBM has significantly increased over the past two decades, reaching a peak at 35 articles in 2022. This trend aligns with the rapid growth of complementary and alternative medicine within the healthcare sector. Over the same period, this field has seen substantial expansion across modern societies [37]. Similarly, veterinary medicine has experienced a notable shift, with pet owners increasingly prioritizing the health and well-being of their animals [38]. This change in perspective has driven a growing interest in modern therapeutic tools for treating and managing various pathologies in animals.

The top terms with the highest TF-IDF scores, ranked by weight and closely related in meaning, suggest that the primary research areas concerning PBM likely focus on its cellular effects, pain management, and treatment of wound, tissue injuries, oral and skin lesions, bone pathologies, or diabetic-related lesions. Additionally, the frequent occurrence of the term "acupuncture" highlights a growing interest in the application of laser therapy in this domain.

The term "cell" appears the most frequently occurring word, which aligns with the predominant focus on "cellular effects of PBM therapy", one of the central topics of areas of investigation.

Regarding to the cellular effects of MLS® laser therapy, a recent study by Pasternak-Mnich et al. [39] showed that MLS® may induce a pro-apoptotic result, related on the duration of laser irradiation. Specifically, when a sufficiently high energy dose and frequency are applied over a prolonged exposure period, intracellular calcium ion concentration and free radical production in mesenchymal stem cells are markedly elevated. However, the precise mechanisms underlying these effects at the cellular and sub-cellular levels remain poorly understood [38]. Moreover, MLS® laser exposure has been shown to influence liposome fluidity and stability, with the potential to induce structural and functional changes in the cell membrane, depending on the parameters used [40].

In the context of pain management, previous studies have demonstrated significant improvements in both knee function and reductions in pain among patients with osteoarthritis receiving MLS® laser irradiation. Moreover, when combined with physiotherapy exercises, MLS® therapy has shown potential clinical advantages over other rehabilitation modalities for subacromial pain syndrome, resulting in a substantial reduction in pain and functional disability [41, 42].

Similarly, in the treatment of chronic neck pain, MLS® laser therapy in conjunction with exercises has proven to be more effective than other forms of LLLT [25]. For patients with chronic non-specific low back pain, MLS® therapy yields a comparable reduction in both pain and disability [43].

On a molecular level, MLS® laser irradiation has been shown to significantly increase the expression of NLRP10, an anti-inflammatory protein that inhibits the production of interleukins IL-1β and IL-18 [44]. The rapid analgesic effect observed in animal models of persistent pain suggests that the analgesic properties of MLS® laser therapy may also be attributable to its influence on the production of antinociceptive substances (such as endorphins), modulation of peripheral nerve conduction, and inhibition of nociceptive stimulus transmission [45].

Compared to LLLT, MLS® lasers are characterized by an average power exceeding 500 mW and by the simultaneous emission of two specific wavelengths: 808 nm and 905 nm. This dual-wavelength configuration has been investigated in preclinical models of peripheral nerve injury. In a randomized, double-blind study on rats undergoing end-to-side neurorrhaphy, Gigo-Benato et al. [23] reported that the combined use of continuous 808 nm and pulsed 905 nm irradiation produced significantly greater improvements in functional recovery, muscle mass preservation, and nerve fiber regeneration compared to either wavelength alone.

Moreover, the use of synchronized emissions, combined with gated modes and wide-area scanning, contributes to minimizing surface heating—an essential safety consideration for class IV PBM devices. As highlighted by Zein et al. (2018) [19] and Cronshaw et al. (2023) [20], maintaining tissue temperature below 45 °C is crucial to avoid photothermal damage. This thermal control is achieved by tailoring emission parameters such as duty cycle, wavelength, beam profile, and exposure time per unit area, ensuring that the irradiance remains within biologically tolerable limits.

In the randomized clinical trial by Alayat et al. [46], MLS® laser therapy combined with exercise produced superior improvements in pain and disability in patients with chronic neck pain, compared to a cluster-type LLLT device (BTL 5000) plus exercise. Although both treatments delivered similar fluences (4 J/cm²), the difference in clinical outcomes may be attributed to the optical characteristics of the devices. MLS® used a single, large spot size (~3.14 cm²) with synchronized wavelengths, while BTL 5000 employed multiple small non-overlapping beams. Parker et al. [5] emphasized that beam geometry, spot size, and power output critically affect photobiomodulation efficacy. Cronshaw [15] further noted that large spot sizes with consistent irradiance can improve treatment reproducibility and energy distribution. These findings suggest that optical design—alongside dosimetry—plays a significant role in determining PBM clinical effectiveness, and that similar dual-wavelength or multimodal approaches are increasingly being adopted by other manufacturers (e.g., Summus Medical, K-Laser, LightForce, Pioon).

Significant improvement in post-burn lesion pain has also been reported in the literature. After ten laser sessions of MLS® laser therapy, a marked reduction in pain was observed, with a significant decrease occurring after the first two sessions, followed by continuous pain reduction throughout the treatment period [21].

The effects of other forms of photobiomodulation (PBM), also referred to as LLLT, on pain management have been widely studied in various conditions, including myofascial pain in the trapezius muscle, a human oral capsaicin pain model, knee osteoarthritis [47], experimental tendinitis in sheep [48], pain following canine cruciate ligament repair [49], gingivostomatitis [50], diabetic leg ulcers [51], and oral ulcers [52]. Further studies are warranted to explore the potential benefits of MLS® therapy in these conditions.

In the context of wound and tissue injury treatment, it is well-established that MLS® therapy enhances cellular energy metabolism, supports the repair processes, and promotes angiogenesis and collagen remodeling [44]. Additionally, a previous study high-lighted the anti-inflammatory properties of a MLS®, which has been commonly used to facilitate healing, reduce inflammation, and alleviate pain [53].

Further research is needed to refine specific treatment protocols using MLS® therapy for different phases of the healing process, potentially optimizing its clinical benefits in wound management and tissue repair.

Relating to laser acupuncture, the scientific literature on the subject has grown extensively and the fundamentals of laser acupuncture are now well defined. Recent studies have established that laser light can be applied effectively, efficiently and securely in acupuncture treatments and it might be an alternative to needle acupuncture. However, many questions remain unanswered concerning the optimal parameters and effects of this innovative approach [54]. Notably, MLS® laser acupuncture has recently been employed with success in alleviating symptoms in patients with Bell's palsy [55], and has shown clinical benefits in the treatment of adolescent idiopathic scoliosis [56].

An intriguing association has been noted between the words "bone" and "euthanasia" in the context of veterinary care. For instance, dogs suffering from osteoarthritis [57] or degenerative myelopathy are often euthanized when they become nonambulatory and incontinent, as these conditions pose significant challenges for home care. PBM should be considered as a palliative intervention to manage symptoms, improve quality of life and, and potentially increase the survival time of dogs in such cases [58].

Additionally, the frequent co-occurrence of the terms "cell", "proliferate" and "mesenchym" and/or "stem" reflects ongoing research into the ability of MLS® laser irradiation to modulate mesenchymal stem cells (MSCs) for therapeutic purposes [59].

This research identified the most significant MLS®-focused studies within the field of PBM. The trending topics that have the highest number of publications were closely interrelated, with "PBM therapeutic uses" emerging as the most prominent. In addition to the therapeutic applications previously discussed, it is noteworthy to highlight the use of the MLS® laser in the early stages of acute respiratory distress syndrome (ARDS) related to COVID-19 [60]. In this context, the MLS® laser treatment improved lung function and overall clinical status, reducing the need for mechanical ventilation and shortening intensive care unit (ICU) stays However, confirmation of the effects of PBM therapy in COVID-19 pneumonia requires further validation in larger clinical trials [60].

Another key topic is "pain control with PBM" which is closely linked to "PBM effects on cells and its mechanism of action". Additional important areas include the use of PBM in oral pathologies. Despite the frequent occurrence of the terms like "wounds" and "bone", research on "laser PBM on wounds and bone" was identified as a less explored topic. Nonetheless, growing interest in these subjects has been observed, reflecting their increasing relevance in recent years.

It is essential to acknowledge the limits of the methodology used in this review. First, the exploration terms employed may not have captured all possible synonyms, potentially leading to the exclusion of relevant studies. Furthermore, the comprehensive of review may have been limited by the omission of documents not indexed in the Scopus® database. The inclusion criteria, such as requiring abstracts to be in English and applying specific screening standards, may have also influenced the number of articles reviewed. Despite these limitations, this review provides valuable insights into PBM, shedding light on key issues and uncovered questions, particularly in relation to MLS® laser therapy in PBM.

Conclusions

In this review, machine learning techniques were utilized to analyze the existing literature on the application of PBM in medical settings, with a particular focus on MLS® laser therapy. The results revealed a notable increase in research activity surrounding this topic, reflecting a growing interest and heightened focus within the scientific community.

The clinical relevance of this review lies in its ability to map the current state of photobiomodulation research, especially in relation to MLS® laser therapy, across both human and veterinary medicine. The findings support the growing interest in PBM as a complementary non-invasive therapeutic option for managing musculoskeletal disorders, chronic pain, wound healing, and neuropathic conditions. Furthermore, this synthesis highlights the need for standardized treatment parameters and stronger clinical evidence, thus offering a foundation for future protocol development and personalized laser therapy approaches.

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